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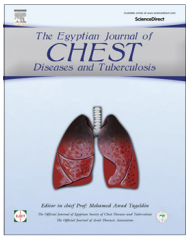

ORIGINAL ARTICLE

Diagnostic and prognostic role of procalcitonin in CAP

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KEYWORDS

Community-acquired pneumonia;
Biomarkers;
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Abstract Despite advances in antimicrobial therapy, CAP remains the seventh leading cause of death in USA. Procalcitonin (PCT) is the pre-hormone of calcitonin, which is normally secreted by the C cells of the thyroid in response to hypercalcemia, its concentration was significantly increased in CAP. In lower respiratory tract infections, measuring serum PCT may aid physicians in differentiating between typical bacterial and non-bacterial causes of inflammation, using a cut-off value of 0.5 ng/mL and serum PCT guidance can reduce total antibiotic use. Furthermore, serum PCT is useful in predicting bacteraemia and in assessing disease severity in CAP patients.

Aim of the work: To determine the usefulness of procalcitonin as a predictor of etiology and prognosis in patients with CAP.

Patients and methods: This study was conducted at Tanta University Hospital over 50 patients with clinical and radiological findings compatible with CAP, 25 mild and moderate CAP and 25 severe pneumonia, thorough history taking, full Clinical examination, plain Chest X-ray, arterial blood gases, sputum samples for Gram stain and culture, blood samples for procalcitonin level measurement by monoclonal immunoluminometric assay was done.

Results: There was a statistically significant rise of PCT in severe CAP as its mean levels were 4.7 ± 0.5 and 11.9 ± 27 ng/ml in mild and severe CAP groups respectively, with a positive correlation between the level of PCT and the severity of CAP. There was a statistically significant rise of PCT in typical pneumonia with a mean level of 9.9 ± 2.24 ng/ml in comparison to atypical pneumonia with a mean level of 3.2 ± 1.96.

Conclusion: PCT measurement may provide an important indicator of severity for patients with CAP, also it can assess treatment response in these patients.

Introduction

Despite advances in antimicrobial therapy, rates of mortality due to pneumonia have not decreased significantly. Patients with certain coexisting illnesses as COPD, diabetes mellitus, congestive heart failure (CHF), coronary artery disease, active

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malignancy, immunosuppression, chronic liver and renal disease, have an increased incidence and mortality of CAP.

CAP is defined as "an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales), in a patient not hospitalized or residing in a long-term care for more than 14 days before the onset of symptoms. Most patients have nonspecific symptoms such as fatigue, headache, myalgia, anorexia and symptoms of pneumonia may include fever or hypothermia, sweating, rigors, dyspnea, chest discomfort, new cough with or without expectoration, or a change in the color of sputum in patients with chronic cough [1,2].

First data regarding the increasing procalcitonin (PCT) concentration in the blood during inflammation were obtained by a group of French military doctors (Dr. Carsin, etc.), who studied markers of acute lung injury in patients with extensive burns; its concentration was significantly increased in many cases.

Retrospective analysis revealed that patients with the highest levels of procalcitonin in blood had infectious complications, including sepsis and septic shock [3].

PCT is the pre-hormone of calcitonin, which is normally secreted by the C cells of the thyroid in response to hypercalcemia; under normal conditions, negligible serum PCT concentrations are detected [4]. The mechanism proposed for PCT production after inflammation and its role are still not completely known. It is believed that PCT is produced by the liver [5] and peripheral blood mononuclear cells [6], modulated by lipopolysaccharides and sepsis-related cytokines.

Among several markers of inflammation and sepsis, PCT is studied to investigate its role and accuracy for the diagnosis of bacterial infections. PCT is a 116 amino acid peptide with no known hormonal activity [7]. In lower respiratory tract infections, measuring serum PCT may aid physicians in differentiating between typical bacterial and non-bacterial causes of inflammation, using a cut-off value of 0.5·ng/mL [8] and serum PCT guidance can reduce total antibiotic use [9]. Furthermore, serum PCT is useful in predicting bacteraemia and in assessing disease severity in patients with community-acquired pneumonia [10].

Most children with CAP are treated with antibiotics without determination of the causative agent leading to a considerable over-use of antibiotics that increases the risk of bacterial resistance, the incidence of drug-related adverse events, and therapeutic costs [11]. A number of trials have been made to differentiate viral and bacterial infections, and rationalize antibiotic use by means of easily determined biomarkers [12].

Procalcitonin stands out as one of the most accurate sepsis markers, with a superior diagnostic utility in sepsis compared with C-reactive protein, interleukin-6, and lactate [3,13]. PCT level was more sensitive (88% vs. 75%) and more specific (81% vs. 67%) than CRP level for differentiating bacterial from non-infective causes of inflammation [3].

High procalcitonin concentrations are both sensitive and specific for the diagnosis of sepsis. P. Hausfater et al. evaluated the sensitivity, specificity, and predictive value of the PCT for identifying cases of systemic infection in patients attending an emergency department. PCT concentrations assay were measured in serum samples by use of an immunoluminometric assay (LUMI test PCT; Brahms Diagnostica). The detection limit of the assay was 0.08 ng/mL, and the functional sensitivity (inter assay variation coefficient, 20%) was 0.33 ng/mL. The upper limit of normal was 0.5 ng/mL. All samples were tested in duplicate. They reported that the procalcitonin level has excellent specificity (0.99) but a sensitivity of only 0.35 (with use of a cutoff point of 0.5 g/mL) for the diagnosis of systemic infection. However, lowering the procalcitonin cutoff point to 0.2 ng/mL led to improved sensitivity (0.62) with persistent good specificity (0.88) [14].

Identifying the etiology of community-acquired pneumonia (CAP) is a clinical difficulty because single clinical, radiologic, or laboratory parameters have limited value to predict the infectious organism [3], and no rapid test has been standardized for the diagnosis of "atypical" or viral pathogens, so empirical broad-spectrum antibiotic therapy is usually chosen [4,5]. Serum PCT levels might help clinicians to choose proper antibiotic by differentiating between classic bacterial and atypical or viral etiology [15].

Aim of the work

The aim of the work was to determine the usefulness of procalcitonin as a predictor of etiology and prognosis in patients with CAP.

Patients and methods

This study was conducted at Tanta university Hospital over a 12 month period from December 2012 to December 2013 over 50 patients with clinical and radiological findings compatible with CAP, 25 mild and moderate CAP (12 males and 13 females) with a mean age of 47 ± 3.43 years and 25 severe pneumonia (11 males and 14 females) with a mean age of 45 ± 3.21 years. Four were on mechanical ventilation with no mortality.

Inclusion criteria

CAP was defined as an acute illness associated with at least one of the following symptoms as fever, new cough with or without sputum production, pleuritic chest pain, dyspnea, or change in the color of sputum in patients with chronic cough or signs as altered breath sound, rales, plus chest X ray showing an opacity compatible with acute pneumonia [1,2].

Criteria for severe CAP

Minor criteria

(1) Confusion/disorientation.
(2) Respiratory rate >30 breaths/min.
(3) Heart rate >120 beat/min.
(4) Hypotension requiring aggressive fluid resuscitation.
(5) Hypothermia (core temperature, <36 °C).
(6) Multilobar infiltrates.
(7) Leucopenia (WBC count <4000 cells/mm^3).
(8) Uremia (BUN level, >20 mg/dL).
(9) PaO_2/FiO_2 ratio <250.
(10) Thrombocytopenia (platelet count, $<100{,}000$ cells/mm^3).

Major criteria

(1) Invasive mechanical ventilation.
(2) Septic shock with the need for vasopressor.

Other criteria to consider

(1) Hyponatremia.
(2) Cirrhosis, asplenia.
(3) Unexplained metabolic acidosis or elevated lactate level.

Any patient with an acute illness and symptoms suggesting lower respiratory tract infection, including new cough with high fever or chills, pleuritic chest pain, dyspnea, or prolonged fever was evaluated clinically and radiologically. CAP was diagnosed if the patient fulfilled the criteria for pneumonia and the pneumonia had occurred at home or within 48 h of admission to hospital without residence in a long-term care facility.

Exclusion criteria

(1) Patients with a prior hospitalization within 2 weeks of a current diagnosis of pneumonia.
(2) Residence in a long-term care facility.
(3) Antibiotic use in the prior 14 days.

All subjects were subjected to thorough history taking, full Clinical examination, chest X-ray and CT in some cases, routine laboratory investigations, arterial blood gases, sputum sample and tracheal aspirate in mechanically ventilated patients for culture and sensitivity, serology test for *Chlamydia pneumoniae*, Legionella species, *Coxiella burnetii* and *Mycoplasma pneumoniae* a fourfold or greater antibody rise by complement fixation test for definition of atypical pneumonia were performed.

PCT assay requires 20 µl of plasma, 5 ml blood sample collected within the first 24 h of admission, centrifuged, and frozen at −80 °C until analyzed. PCT levels were measured by monoclonal immunoluminometric assay (Liaison Brahms PCT; Brahms Diagnostica GMBH; Berlin, Germany). This immunoluminometric assay is based on the reaction of two antigen-specific monoclonal antibodies that bind PCT (as an antigen) to calcitonin and katacalcin segments. The inter-assay precision of the kit is 3–6.6%, the lower limit of detection is 0.02 ng/mL and the normal range is less than 0.5 ng/mL [16].

All patients were followed up for at least 4 weeks or until death. A repeat chest X-ray and blood sample for PCT assay were obtained from 2 to 4 weeks after the initial diagnosis of CAP.

Results

There were no significant differences regarding age and sex between the 2 studied groups but there was statistical significant rise of PCT level in severe CAP (group II) than mild CAP (group I) (Tables 1 and 2).

Table 1 Baseline characteristics and serum PCT levels in the studied groups.

	Group 1	Group II	*P*
Age	47 ± 3.43	45 ± 3.21	NS
Male	12	11	Ns
Female	13	14	N S
Serum PCT level ng/ml	4.7 ± 0.5	11.9 ± 27*	S*

* Significant.

Table 2 Statistical comparisons of serum PCT (ng/ml) in typical and atypical CAP.

	Serum prolactin (ng/ml)	
	Atypical pneumonia	Typical pneumonia
Range	02.5–3.9	4.5–14.3
Mean ± SD	3.2 ± 1.96	9.9 ± 2.24*
t Test	7.33	
P	< 0.001	

* Significant.

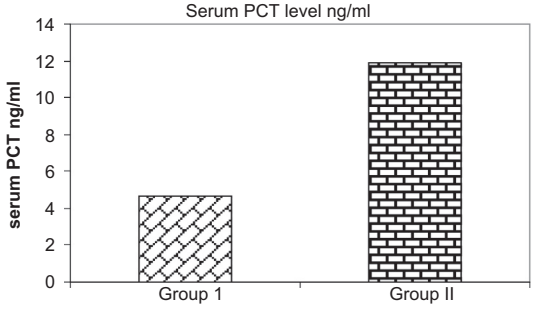

Figure 1 Statistical comparisons of serum levels of PCT in mild (group I) and severe (group II) CAP.

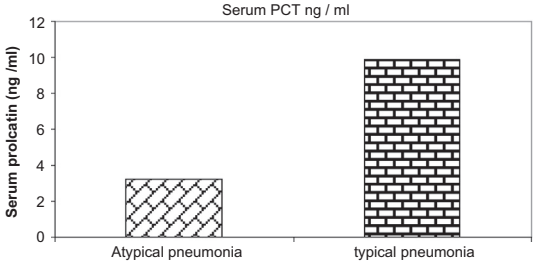

Figure 2 Statistical comparisons of serum PCT (ng/ml) in typical and atypical CAP.

There was a statistical significant rise of PCT in typical pneumonia with a mean level 9.9 ± 2.24 ng/ml in comparison to atypical pneumonia with a mean level 3.2 ± 1.96 ng/ml (Figs. 1–3).

There was positive correlation between the level of PCT and the severity of CAP.

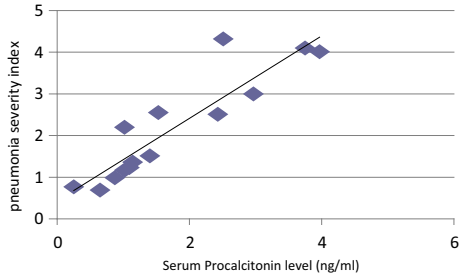

Figure 3 Correlation between serum procalcitonin and severity of pneumonia.

Discussion

F Moulin et al. found that PCT concentration, with a threshold of 1 μg/l is more sensitive and specific and has greater positive and negative predictive values than CRP, IL-6, or white blood cell count for differentiating bacterial and viral causes of CAP in untreated children admitted to hospital as emergency cases. Previous studies of community-acquired pneumonia reported that the highest pro-calcitonin concentrations were in patients with pneumonia due to classic bacterial pathogens, rather than in patients with atypical or viral pneumonia [17,18].

Etiologic diagnosis of febrile patients who present to an emergency department is complex and sometimes difficult. Physicians have to identify and often rapidly treat patients with systemic infection. as most microbiological test results are not available for 24 h, a sensitive and specific marker of systemic infection would be useful [19]. In 1993, Assicot et al. reported a correlation between a high serum level of procalcitonin and sepsis [20].

It has been reported that serum PCT determination may help to discriminate between septic and non-septic underlying disease in ARDS [21]. However, a more recent study concluded that serum PCT cannot reliably differentiate sepsis from non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients [22]. At present, there are few data addressing the usefulness of PCT to predict etiology in patients with CAP [18]. Recently, Christ-Crain et al., [23] found that a procalcitonin-based therapeutic strategy was useful to reduce antibiotic use in lower respiratory tract infections, based on the ability of PCT to discriminate between patients with or without clinically relevant bacterial infection. Similarly, PCT serum levels were found to be higher in bacterial versus viral or atypical etiologies in two studies of CAP [17,18]. In contrast, in other studies [8,24–26], no differences were found in PCT levels between bacterial and nonbacterial etiologies. The results of studies on pneumonia suggest that PCT is a good predictor of the disease severity. After admission to the hospital, patients' serum total PCT progressively declined concomitantly with the clinical resolution of the pneumonia; at discharge, on discharge the patients who had persistent radiographic abnormalities had significantly higher levels than did those who had complete resolution [8,27]. The most precise way to diagnose bacterial infections is by culture; tests to confirm viral infections include determination of acute and convalescent phase antibody titers and tests for viral antigens. However, there is often a delay until results are known, and rapid immunological or genomic tests require prior knowledge of the infectious agent. The identification of markers for the early recognition of bacterial infections could guide treatments, reduce misuse of antibiotics, and possibly improve long-term outcomes [28]. In HAP, CAP and, to a lesser extent, AECB, but not TB, significantly elevated median PCT levels were found compared to controls. However, median PCT levels in all groups were below the recommended cut-off level of 0.5 ng/mL. Therefore, according to the present study, PCT concentration seems not to be particularly useful for the detection of lower respiratory tract infections.

In the recent publication of Brunkhorst et al. reported elevated PCT levels in patients with severe pneumonia; also PCT concentration was found to be of moderate prognostic value [29]. Concerning the usefulness of PCT concentration as a diagnostic parameter, Hausfater et al. [14] showed that sensitivity was low (in contrast to a high specificity) with the use of a cut-off level of 0.5 ng/mL, but that improved sensitivity could be obtained after reducing the cut-off level. They concluded that the PCT threshold could be lower than that proposed for critically ill patients. Similar results were seen in the present study, in which PCT levels showed significantly elevated values below the cut-off level in patients with severe CAP compared to the mild group. However, Hausfater et al. included patients from an emergency department who had heterogeneous infectious diseases. It was suspected that PCT could be useful for screening emergency-department patients with more severe infections, since good correlation of PCT concentration was seen with the prognosis of patients suffering systemic infections [14].

Furthermore, Fleischhack et al. [30] found a higher sensitivity and specificity of PCT in comparison to CRP in the diagnosis of high-risk Gram-negative bacteremia in neutropenic pediatric patients. PCT concentration is believed to be a sufficient parameter for differentiation between severe systemic bacterial and nonbacterial infections [31]. These results agree with the present study, as PCT concentration was significantly higher in typical pneumonia than atypical one. A similar conclusion was drawn by Toikka et al. [24] who reported a significant rise in PCT levels in children with bacterial than viral pneumonia and it was in the case pertaining to the extreme value in the CAP group, the clinical condition of the patient was found to deteriorate progressively. As a result, in later stages, the criterion of sepsis was evident, explaining the high level of PCT [20]. Castelli et al. reported that patient deteriorating progressively with evident criteria of sepsis, had a high PCT level, with a positive correlation between serum PCT concentration and the severity of infection, clinical course, and mortality [32].

Conclusion

PCT measurement may provide an important indicator of severity for patients with CAP, also it can assess treatment response in these patients.

Conflict of interest

There is no conflict of interest.

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